federal register

TUESDAY, DECEMBER 7, 1976

PART V:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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ORAL CONTRACEPTIVE DRUG PRODUCTS

Notice and Proposal of Revised Physician and Patient Labeling

DEPARTMENT OF HEALTH EDUCATION, AND WELFARE

[Docket No. 76N-0487]

Food and Drug Administration

[21 CFR Part 310]

ORAL CONTRACEPTIVES

Patient Labeling Revision

The Food and Drug Administration (FDA) is proposing to revise the requirements for patient labeling for oral contraceptives. Information in the labeling would be expanded, and this new labeling would be provided to each patient to whom the drug is dispensed. Interested persons have until February 7, 1977 to submit comments.

The present regulation under § 310.501 (a) (21 CFR 310.501(a)) requires two types of patient labeling: (1) Patient package information to be provided to each patient when the drug is dispensed, furnishing brief information about the nature of the drug, the need for continuing medical supervision, and the availability of more detailed information (a booklet) from the physician; and (2) A booklet available to a patient upon request to her physician. At present, the full text of the patient package information is set forth in § 310.501(a)(4) of the regulation; but only an outline of the kinds of information to be included in the booklet is contained in § 310.501(a)(6) of the regulation.

The patient labeling requirements for oral contraceptives in § 310.501(a) have not been substantially revised since they were published in the FEDERAL REGISTER of June 11, 1970 (35 FR 9001). In 1975, FDA conducted a survey among 1,720 users and 949 former users of oral contraceptives to obtain information about the use of and the need for patient labeling for these products. One of the significant findings of this survey was the finding that 81 percent of the users polled wanted more information on common side effects, and 73 percent wanted more details on warnings and precautions. This is consistent with criticism voiced by consumer groups and individual consumers to the effect that current patient labeling does not contain enough information. Copies of the survey ("Consumer Perceptions of Patient Package Inserts for Oral Contraceptives," order number is PB248-739/SET/AS), mentioned above are available from the National Technical Information Service, U.S. Department of Commerce, P.O. 1553, Springfield, Va. 22151, at a paper cost of $18.00 per copy.

Patient labeling for oral contraceptives is based on the approved physician labeling for these drug products. Elsewhere in this issue of the FEDERAL REGISTER under Docket No. 75N-0304, the Commissioner of Food and Drugs is issuing a notice specifying new physician labeling for oral contraceptives. The new labeling includes significant new information concerning thromboembolic and thrombotic disorders, carcinoma, and effects on the exposed fetus. The Commissioner concludes that the patient labeling should be revised to conform to the new physician labeling and that the more detailed patient labeling, previously available only on request from the physician, should be furnished by the dispensor to each patient to whom the drug is dispensed.

The practice of FDA has been to include the text of the patient package insert in the agency's regulations. This requires that the statutory notice-and-comment rule making procedure be utilized whenever a significant change is sought in the text of the labeling. The experience of FDA has been that the use of this approach in establishing an appropriate text for patient labeling is slow and cumbersome, particularly because of the large numbers of comments that are often received when patient labeling is proposed, and because publication of a final regulation with a delayed effective date is required. The Commissioner has found, moreover, that most of the comments received on patient labeling have been concerned with editorial style rather than substantive issues. He therefore concludes that, while public participation in formulating labeling is worthwhile, the long delays in providing patients with important information on prescription drugs that have occurred as a result of the use of the notice-and-comment approach are unjustifiable.

Accordingly, the Commissioner proposes to utilize the procedure proposed for patient labeling for estrogens for general use published in the FEDERAL REGISTER of September 29, 1976 (41 FR 43108), whereby the regulations will specify only a list of specific items of informaiton that must be included in patient labeling, while a separate FEDERAL REGISTER notice will contain precise language that will be considered by the Commissioner to meet the requirements of the regulation. The public is nonetheless invited to comment on the text of the patient labeling. The comments will be considered; if the text of the labeling is revised, it will be published in a subsequent notice. The Commissioner believes this approach will significantly expedite the revision of patient labeling to provide new information, and still allow for public participation in the process. A notice containing such labeling is published elsewhere in this issue of the FEDERAL REGISTER.

In this notice, the Commissioner proposes to amend § 310.501(a) to require that patient labeling contain, in lay language, information on the effectiveness, contraindications, warnings, precautions, and adverse reactions of oral contraceptives. This information would be presented to the patient in two labeling pieces: (1) a brief summary of certain essential points of information that would be included in the package dispensed to the patient, and (2) a longer, more detailed labeling piece that would accompany or be included in the package dispensed to the patient. As revised, § 310.501(a) would not contain the text of either patient labeling piece but would contain a listing of specific items of information that must be included in the labeling.

The Commissioner has given careful consideration to the advantages and disadvantages of requiring a brief summary and a separate, longer, detailed labeling piece as opposed to requiring only the longer labeling. He has tentatively concluded that the two labeling pieces would be more useful to the patient for the following reasons: (1) The summary is short enough to be included within the package dispensed to the patient and would be more likely to be available to the patient throughout the life of the package and (2) The summary can be quickly and easily read by the patient, will call her attention to the longer labeling piece, and will urge her to read the complete labeling.

The Commissioner recognizes, however, that there may be some disadvantages to requiring the brief summary. The presence of the brief summary labeling may result in some patients reading only the summary and ignoring the longer labeling piece. It may also increase the burden on the pharmacist and the manufacturer, particularly in the case of drugs dispensed from bulk packages, in that two, separate labeling pieces will have to be furnished to the patient. The Commissioner invites interested persons to comment specifically on this aspect of the proposal to assist him in determining which method would be most useful to the patient.

The survey of users of oral contraceptives discussed in the preamble above also revealed that while almost 93 percent of the current users of oral contraceptives reported having received patient labeling, many of those who did not receive the labeling probably had the drug dispense to them from bulk packages rather than from packages of the type intended for the user. This suggests a need for clarification and strengthening of the regulations requiring that bulk packages intended for multiple dispensing include a sufficient number of patient labeling pieces to assure that they can be included with each package dispensed to the patient.

The proposed revision specifies that patient labeling in the form of a brief summary and a longer, detailed labeling piece would be provided by the manufacturer, repacker, relabeler, or distributor. The Commissioner recognizes that the packaging of oral contraceptives is somewhat unusual in that the package to be dispensed by the pharmacists is ordinarily supplied, along with necessary labeling instructions, by the manufacturer or other supplier. The brief summary would be included in each such package dispensed to the patient. The detailed labeling would be a separate leaflet, printed in a typeface that is not condensed and no smaller than 9-point type, and would accompany or be in each package dispensed to the patient. In the case of oral contraceptive drug products in bulk packages intended for multiple dispensing, each bulk package would include a sufficient number of patient labeling pieces to assure that a copy of each can be included with each package dispensed to every patient. The dispensor would

then be responsible for providing the patient with the labeling pieces. Failure to do so would result in the misbranding of the drug product by the dispensor.

The Commissioner advises that he proposes to make the final regulation revising § 310.501(a) effective 60 days after its date of publication in the FEDERAL REGISTER. Manufacturers and suppliers are advised, and the proposed rule provides, that the language in the accompanying notice under Docket No. 75N–0304 published elsewhere in this issue of the FEDERAL REGISTER will be considered by the Commissioner to meet the requirements of the final regulation revising § 310.501(a) for 60 days after its effective date, i.e., 120 days after date of publication, notwithstanding that changes in the wording of the patient labeling may be made in the final regulation revising § 310.501((a) or in the notice accompanying this proposal, as a result of coments received from the public, or as a result of new information. Thus, manufacturers may put into use immediately, without advance approval by FDA, the recommended patient labeling, and continue to use that labeling for 60 days after the effective date, i.e., 120 days after date of publication of the final regulation revising § 310.501(a). The Commissioner encourages manufacturers to provide this revised patient labeling in this fashion. He considers it in the interest of the public health that the revised patient labeling be provided to patients as soon as possible. A manufacturer or supplier who defers preparing revised patient labeling until the final regulation is published will have 60 days from the date of publication to implement the new labeling requirement.

Supplements to approved new drug applications that provide for the revised patient labeling shall be submitted under § 314.8 (21 CFR 314.8) within 60 days after the effective date of the final regulation revising § 310.501(a). The changes that are provided for by these supplements will not have a substantial effect on the quality of the human environment; therefore, they need not be accompanied by environmental impact analysis reports.

On or after the effective date of the final regulation, no person would be permitted to introduce or deliver for introduction into interstate commerce, or to hold for sale after shipment in interstate commerce, any oral contraceptive drug product unless the labeling of that product complies with the requirements set forth in the regulation. However, the Commissioner would consider an oral contraceptive drug product packaged before the effective date to comply with the regulation if an adequate number of copies of the revised detailed patient labeling piece (i.e., the detailed patient labeling set forth in Docket No. 75N–0304 appearing elsewhere in this issue of the FEDERAL REGISTER) are furnished to wholesalers or retailers to permit any retail purchaser to obtain such labeling with the product on or after the effective date. This will assure that on or after the effective date of the final regulation all retail purchasers of the product will receive the detailed labeling piece. However, the brief summary patient labeling required by the final regulation would be included only in products packaged after the effective date of the final regulation. Products packaged before the effective date of the final regulation and dispensed on or after the effective date would contain the brief patient labeling currently provided for by § 310.501(a) and be accompanied by the detailed patient labeling required by this proposed revision. These procedures will obviate the necessity of manufacturers recalling products already in distribution channels on the effective date of the final regulation, and repackaging these products to include the brief insert, but will nevertheless assure that on or after the effective date all retail purchasers of the drug will receive the revised, detailed patient information.

(Secs. 502(a), 505, 701(a), 52 Stat. 1050–1053 as amended, 1055 (21 U.S.C. 352(a), 355, 371 (a))) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262))

It is proposed that § 310.501 be amended by revising paragraph (a) to read as follows:

§ 310.501 Preparations for contraception; labeling directed to the patient.

(a) *Oral contraceptives.* (1) The Commissioner of Food and Drugs concludes that the safe and effective use of oral contraceptive drug products requires that patients be fully informed of the benefits and risks involved in the use of these drugs. Information concerning effectiveness contraindication, warnings, precautions, and adverse reactions must be furnished to each patient receiving oral contraceptives. This information shall be given to the patient by the dispensor in the form of a brief summary of certain essential information included in each package dispensed to each patient, and in a longer, detailed labeling piece in or accompanying each package dispensed to each patient.

(2) The brief summary shall specifically include the following:

(i) A statement that oral contraceptives are effective, but that any deviation from recommended dosage increases the chance of pregnancy.

(ii) A statement of the specific items of history to be told the physician that would lead the physician not to prescribe oral contraceptives (i.e., the contraindications to use).

(iii) A statement that oral contraceptives should be taken only under the continued supervision of a physician.

(iv) A listing of the serious side effects of oral contraceptives such as thrombophlebitis, pulmonary embolism, retinal artery thrombosis, stroke, benign hepatic adenomas, induction of fetal abnormalities, and gallbladder disease.

(v) A statement of the most common side effects such as nausea and vomiting, weight change, change in menses, and breast tenderness.

(vi) A statement that although the estrogen in oral contraceptives causes breast cancer and other cancers in certain animals, it isn't known whether or not oral contraceptives can cause cancer in humans.

(vii) A statement that oral contraceptives are of no value in the prevention or treatment of venereal disease.

(viii) A statement calling attention to the detailed patient labeling and a recommendation that it be carefully read.

(3) The detailed patient labeling shall be a separate printed leaflet independent of any additional materials, in a typeface that is not condensed and no smaller than 9-point type. It shall specifically include the following:

(i) Name of the drug.

(ii) Name and place of business of the manufacturer, packer, relabeler or distributor.

(iii) A statement that oral contraceptives are effective but can cause certain serious side effects.

(iv) A statement that oral contraceptives should be taken only under the continued supervision of a physician.

(v) A statement of the effectiveness of oral contraceptives, including the differences in effectiveness among different types and the relationship between effectiveness and estrogen dosage.

(vi) A summary of the effectiveness of other methods of contraception.

(vii) A warning regarding the serious side effects of oral contraceptives, including the relative risk (where known) faced by users compared to nonusers and the relationship of the side effects to age and/or other conditions. The side effects mentioned must include thrombophlebitis pulmonary embolism, retinal artery thrombosis, stroke, (the relation of these to estrogen dose is to be mentioned), benign hepatic adenomas, induction of fetal abnormalities, and gallbladder disease. The ability of estrogen to cause malignant tumors in animals, endometrial cancer in women, and the evidence that sequential oral contraceptives may increase the risk of endometrial cancer in women must be mentioned. There shall also be a statement that studies of an association between oral contraceptives and breast cancer are largely negative except for a suggestion of increased risk (1 study) in women with benign breast disease, and that there is no evidence of an increased risk of uterine cancer in users of oral contraceptives other than sequentials.

(viii) A statement of common side effects, including nausea and vomiting, weight change, darkening of the skin, changes in menses, and a statement of other serious side effects, including worsened migraine, and worsened heart or kidney disease due to fluid retention, growth of uterine fibroid tumors, depression, jaundice, blood pressure elevation, decreased glucose tolerance and elevated blood lipids.

(ix) A statement of reported side effects not definitely related to oral contraceptive use.

(x) A statement cautioning the patient to consult her physician before resuming the use of the drug after child-

birth, especially if she intends to breast-feed the baby, pointing out that the hormones in the drug are known to appear in the milk and may decrease the flow.

(xi) A comparison of the risk of death from various contraceptive methods (oral contraceptive, IUD, condom or diaphragm, condom or diaphragm with abortion in the event of pregnancy, no contraception but abortion in the event of pregnancy, and no contraception or abortion).

(xii) A statement of the specific items of history to be told the physician which would lead the physician not to prescribe oral contraceptives (i.e., the contraindications to use).

(xiii) A statement of specific items of history that might cause the physician to suggest another method (e.g., risk factors for myocardial infarction, family history of breast cancer or past history of fibrocystic disease or abnormal mammogram, gallbladder disease) or would require the physician's special attention (e.g., migraine, asthma, epilepsy, heart or kidney disease, fibroids, history of depression).

(xiv) A statement that jaundice, depression, breast lumps, and the particular warning signals of thromboembolic disease, thrombotic disease, and ruptured hepatic adenoma, should be reported to the physician.

(xv) A statement of how to take oral contraceptives properly and what to do in the event of one or two missed periods.

(xvi) The date, identified as such, of the most recent revision of the labeling prominently placed immediately after the last section of such labeling.

(4) Patient labeling for each oral contraceptive drug product shall be provided to the retailer by the manufacturer, packer, relabeler, or distributor as follows:

(i) The brief summary patient labeling shall be included in each package intended to be dispensed to the patient.

(ii) The detailed patient labeling shall be included in or shall accompany each package intended to be dispensed to the patient.

(iii) In the case of oral contraceptive drug products in bulk packages intended for multiple dispensing, each bulk package shall include a sufficient number of patient labeling pieces to assure that both pieces can be furnished with each package dispensed to every patient. Each bulk package shall be labeled with instructions to the dispensor to include both patient labeling pieces (the brief summary to be in the package and the detailed labeling piece either in or accompanying the package) with each package dispensed to the patient.

(5) An oral contraceptive drug product that is not labeled as required by paragraph (a) of this section and that is either introduced or delivered for introduction into interstate commerce, or held for sale after shipment in interstate commerce is misbranded under section 502 of the act. However, an oral contraceptive drug product package before the effective date of this paragraph is not misbranded if adequate numbers of copies of the detailed patient labeling required by this paragraph are furnished to wholesalers or retailers to permit any retail purchaser after the effective date to obtain such labeling with the product.

(6) The Food and Drug Administration has available patient labeling for oral contraceptive drug products that includes information responsive to all the items specified in paragraph (a) (2) and (3) of this section. The labeling has been published in the FEDERAL REGISTER and updated versions will continue to be published as guides when changes occur. Any person may rely on the newest version of this labeling as complying with paragraph (a) (2) and (3) of this section after the effective date of this paragraph.

NOTE: For a period of 60 days after February 7, 1977 any person may also rely on, as complying with paragraph (a) (2) and (3) of this section, the labeling in the notice under Docket No. 75N-0304 published in 41 FR 53633, December 7, 1976.

(7) Holders of new drug applications for oral contraceptive drug products that are subject to paragraph (a) of this section must submit supplements under § 314.8 of this chapter to provide for the labeling required by paragraph (a) (2) and (3) of this section on or before February 7, 1977. The labeling may be put into use without advance approval by the Food and Drug Administration.

Interested persons may, on or before February 7, 1977, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comment (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A-107. A copy of the inflation impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: December 3, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc.76-36029 Filed 12-3-76;1:01 pm]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 75N-0304]

Food and Drug Administration

ORAL CONTRACEPTIVE DRUG PRODUCTS

Physician and Patient Labeling

The Food and Drug Administration (FDA) is issuing revised physician and patient labeling as a guide for manufacturers and distributors of oral contraceptive drug products and is seeking comment on this labeling. Interested persons are invited to comment on the labeling on or before February 7, 1977. All comments will be considered; if the labeling is further revised, the text of the labeling will be published in a subsequent notice.

The need for revised physician and patient labeling arises principally from new information concerning thromboembolic disorders, other vascular problems, carcinoma, and effects on the exposed fetus. The Food and Drug Administration is charged with assuring that drugs are safe and effective for their intended use, and that their labeling provides adequate information for such use and is not false or misleading. The full disclosure of information to physicians concerning such matters as effectiveness, contraindications, warnings, precautions, and adverse reactions is an important element in the discharge of that responsibility.

The statutory scheme anticipates that new information concerning the safety and effectiveness of marketed drugs may require that FDA prescribe changes in their labeling to reveal limitations on use or warn of previously unanticipated hazards.

Significant new information has been reported concerning thromboembolic disorders, other vascular problems, carcinoma, and effects on an exposed fetus associated with the use of oral contraceptive drug products. This has generated a need for a revision of the labeling to inform physicians and patients of these findings. The scientific papers that are the source of this new information are cited in the bibliography given in the revised physician labeling herein. Copies have been placed on file in the office of the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

To ensure maximum public participation in the development of the revised physician labeling for oral contraceptive drug products, a draft of the revised labeling was circulated to various professional, scientific, trade, and consumer organizations. A copy of the draft was placed on public display in the office of the Hearing Clerk, Food and Drug Administration, and notice of its availability was published in the FEDERAL REGISTER of October 24, 1975 (40 FR 49813). The draft labeling was sent to all who requested it.

Forty-three responses on the draft labeling were received from physicians, professional societies, drug manufacturers, and individual consumers. The labeling has also been reviewd and commented on by FDA's Obsterics and Gynecology Advisory Committee. The comments have all been reviewed, and a number of the suggested changes have been adopted in the labeling.

It has been alleged that oral contraceptives are dangerous for use by patients with a family history of breast or uterine cancer. Therefore, FDA considers it advisable to address in this FEDERAL REGISTER notice its position with regard to this issue.

Women with an immediate familial history (mother-daughter) of breast cancer appear to have an increased risk of developing this malignancy during their lifetime. It has been estimated that these women are four times more likely to have breast cancer than those without such a history. There is not, however, adequate scientific evidence that this risk is further enhanced in such individuals by the use of oral contraceptives. At the present time, therefore, contraindication of the use of oral contraceptives in the patient population is not appropriate since contraindications in drug labeling properly relate to known, rather than speculative hazards. However, on the basis of the increased risk of breast cancer in women with an immediate family history of this disease, the agency has included in the labeling for both physicians and patients a warning that patients with a strong familial history of breast cancer who elect to use oral contraceptives be monitored with particular care. Such careful monitoring is mandatory in view of the fact that if breast cancer should develop in such patients, the use of estrogen-containing drugs should be immediately discontinued because such drugs may very well cause rapid progression of the disease if the malignancy is hormone dependent.

Although there appears to be some familial tendency with regard to the occurrence of uterine cancer (endometrial but not cervical), the relationship is generally regarded as far less striking than that noted for breast cancer. At the present time, there is a lack of scientific evidence that this risk is further increased by the use of oral contraceptives. To contraindicate the use of these drugs in patients with a family history of uterine cancer is therefore unwarranted. Rather, the labeling for both the physician and patient stresses the necessity of periodic physical examinations and instructs the physician that appropriate additional examinations should be done in the event of unexplained vaginal bleeding. The agency also requires that vaginal bleeding of unknown etiology be listed as a contraindication to the use of these drugs until such time as malignancy has been ruled out. With such directives in the labeling, FDA feels adequate precautions have been taken to avoid the use of oral contraceptives in patients in whom uterine cancer is suspected, and that in the event that uterine cancer develops while using oral contraceptives diagnosis can be made promptly, the drug discontinued, and appropriate therapy instituted.

There has also been some question whether estrogens should be contraindicated for use by women who were opposed to diethylstilbestrol during their mothers' pregnancy. Because most oral contraceptives contain estrogen, the same question applies to their use by this patient population. It has been estimated that such women have an increased risk of developing in later life a rare form of vaginal or cervical cancer. This risk has been estimated as not greater than four per 1,000 exposures. However, a much higher percentage of such exposed women have been found to have epithelial changes of the vagina and cervix, known as adenosis, although these changes are histologically benign. It is not known whether such changes are precursors to vaginal malignancy.

At the present time, there are no data available that show that this increased risk of vaginal or cervical malignancy is further increased by the use of oral contraceptives or estrogen. Consequently, there is no scientific basis to support contraindicating the use of oral contraceptives in such patients. Further study is needed to define what role, if any, oral contraceptives play with regard to the occurrence of these malignancies in such a patient population. The agency does believe, and has incorporated statements into the labeling for the oral contraceptives, that such patients should be monitored with particular care if they elect to use oral contraceptives. In the event that such a malignancy should develop while using oral contraceptives, diagnosis could be made promptly, the drugs discontinued, and appropriate therapy instituted without delay.

The patient labeling for oral contraceptives has also been revised to conform to the revised physician labeling. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is proposing to amend § 310.501(a) (21 CFR 310.501(a)) to delete the currently required text of the printed information that accompanies the drug when it is dispensed to patients and to specify the kind of information to be contained in the patient labeling without prescribing its exact wording.

The texts of the revised physician and patient labeling are set forth in this notice. The Commissioner advises that the patient labeling for oral contraceptive drug products specified in this notice complies with the patient labeling requirements proposed in § 310.501(a) and can be relied upon by manufacturers, packers, relabelers, and distributors to meet these requirements.

In the FEDERAL REGISTER of April 7, 1975 (40 FR 15392), the Commissioner proposed new requirements concerning the content and format of all prescription drug labeling, that is, labeling directed to the physician. The Commissioner concludes that the physician labeling set forth below for oral contraceptive drug products is consistent with the proposed prescription drug labeling format. Furthermore, it is consistent with the proposed requirement under § 1.112 (c)(6)(ii) in the April 7, 1975 notice,

that printed patient information be referenced under the "Precautions" section of the physician labeling and reprinted at the end of it.

Because of the impact of the information that has become available on manufacturers, physicians, and patients and the wide use of oral contraceptive drug products, the Commissioner seeks comment on the text of both the full disclosure physician labeling and the patient labeling.

Although comment on the labeling is sought, the importance of the new information is such that the revised labeling for physicians should be put into use without delay. The revised patient labeling may also be used, and its use is encouraged, but since the current patient labeling for these drugs is the subject of a substantive regulation, § 310.501 (a), use of the revised patient labeling may be delayed until the rule making procedure providing for the revision is completed.

The Food and Drug Administration will regard as misbranded and subject to regulatory action, any oral contraceptive drug product that is shipped in interstate commerce by manufacturers, repackers, relabelers, or own-label distributors after April 6, 1977 without labeling which is substantially the same in content as the physician labeling set forth in this notice. However, the physician labeling given below may be edited, e.g., by abbreviating the names of the medical journals in the "References" section, so long as no substantive changes are made in the content of the labeling. Under the provisions of § 314.8(d) (21 CFR 314.8(d)), such labeling may be put into use before approval of a supplement to a new drug application.

Holders of approved new drug applications for oral contraceptive drug products shall submit supplements on or before April 6, 1977 to provide for the revised physician labeling.

The notice of proposed rulemaking, published elsewhere in this issue of the FEDERAL REGISTER for the revised patient labeling proposes that that requirement will become effective 60 days after it is published as a final regulation.

Upon reviewing the comments received on the physician and patient labeling for oral contraceptive drug products if, on the basis of the comments, revisions are necessary, the Commissioner will publish a followup notice giving the revised text of the physician and patient labeling. Notwithstanding changes that may appear in the text of the patient labeling published after the comment period, the labeling that is already in use at the time and the same in content as the text given below may continue to be used for 60 days after the effective date of the revision of § 310.501(a), i.e., for 120 days after publication.

The physician labeling for oral contraceptive drug products is set forth below:

ORAL CONTRACEPTIVE LABELING

DESCRIPTION

(TO BE SUPPLIED BY MANUFACTURER)

(Description should include the following information.)

1. The proprietary name and the established name if any, of the drug product;

2. The same qualitative and/or quantitative ingredient information as required for labels;

3. The pharmacological or therapeutic class of the drug product;

4. The chemical name and structural formula.

CLINICAL PHARMACOLOGY

FOR COMBINATION ORAL CONTRACEPTIVES ONLY

Combination oral contraceptives act primarily through the mechanism of gonadotropin suppression due to the estrogenic and progestational activity of the ingredients. Although the primary mechanism of action is inhibition of ovulation, alterations in the genital tract including changes in the cervical mucus (which increase the difficulty of sperm penetration) and the endometrium (which reduce the likelihood of implantation) may also contribute to contraceptive effectiveness.

FOR PROGESTIN ORAL CONTRACEPTIVES ONLY

The primary mechanism through which (insert name of drug) prevents conception is not known, but progestin-only contraceptives are known to alter the cervical mucus, exert a progestional effect on the endometrium, interfering with implantation, and, in some patients, suppress ovulation. (Manufacturer to include information on absorption, distribution, elimination, and pharmacokinetics if pertinent; also on drug interactions pertinent to human use.)

INDICATIONS AND USAGE

(Insert name of drug) is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Oral contraceptives are highly effective. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than 1 pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of 3 pregnancies per 100 women-years are reported for the progestin-only oral contraceptives.

These rates are derived from separate studies conducted by different investigators in several population groups and cannot be compared precisely. Furthermore, pregnancy rates tend to be lower as clinical studies are continued, possibly due to selective retention in the longer studies of those patients who accept the treatment regimen and do not discontinue as a result of adverse reactions, pregnancy, or other reasons.

In clinical trials with (insert name of drug (insert number of) patients completed _____ cycles and a total of _____ pregnancies were reported. This represents a pregnancy rate of _____ per 100 woman-years. (manufacturer to add other information related to the pregnancy rate with his particular product, if needed to provide adequate prescribing information to the physician.)

The following table gives ranges of pregnancy rates reported in a standard textbook (Ref. 1) for other means of contraception. An individual patient may achieve higher or lower rates with any given method (except the IUD), depending upon the degree of adherence to the method.

PREGNANCIES PER 100 WOMAN-YEARS

IUD, 2–3; condoms, 6–13; diaphragm with cream or gel, 2–33; Coitus interruptus, 6–16; rhythm, 6–19; foams, creams or gels alone, 38–42; no contraception, 60–80.

Epidemiological studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism (refs. 2 and 3). For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptives should be started on preparations containing 50 MCG or less of Estrogen.

CONTRAINDICATIONS

Oral contraceptives should not be used in women with any of the following conditions:

1. Thrombophlebitis or thromboembolic disorders.

2. A past history of deep vein thrombophlebitis or thromboembolic disorders.

3. Cerebral vascular or coronary artery disease.

4. Known or suspected carcinoma of the breast.

5. Known or suspected estrogen dependent neoplasia.

6. Undiagnosed abnormal genital bleeding.

7. Known or suspected pregnancy (see warning No. 5).

WARNINGS

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gall bladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Three principal studies in Great Britain (Refs. 4 through 6) and three in the United States (Refs. 7 through 10 have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause (Tables 1 and 4) than are nonusers. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1 to 3.5 deaths annually per 100,000 users and increases with age (Table 2). In a collaborative American study (Refs. 9 and 10) of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hermorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers (Table 4).

TABLE 1

HOSPITALIZATION RATES DUE TO VENOUS THROMBOEMBOLIC DISEASE (REF. 6)

	Admissions annually per 100,000 women, age 20–44
Users of oral contraceptives	45
Nonusers	5

TABLE 2.—*Death rates due to pulmonary embolism or cerebral thrombosis (Ref. 5)—deaths annually per 100,000 nonpregnant women*

	Age 20 to 34	Age 35 to 44
Users of oral contraceptives	1.5	3.9
Nonusers	.2	.5

An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported (Refs. 11, 12, and 13), confirming a previously suspected association (Tables 3 and 4). These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30–39 year age group and 67 cases per 100,000 women users in the 40–44 age group.

TABLE 3.—*Myocardial infarction rates in users and nonusers of oral contraceptives in Britain (Refs. 11, 12, and 13)—cases annually per 100,000 women*

	Nonfatal		Fatal	
	Age 30 to 39	Age 40 to 44	Age 30 to 39	Age 40 to 44
Users of oral contraceptives	5.6	56.9	5.4	32
Nonusers of oral contraceptives	2.1	9.9	1.9	12
Relative risk	2.7	5.7	2.8	2.8

In an analysis of data derived from several national adverse reaction reporting systems (Ref. 2), British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50–80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States (Ref. 3). Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestin-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk.

The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events.

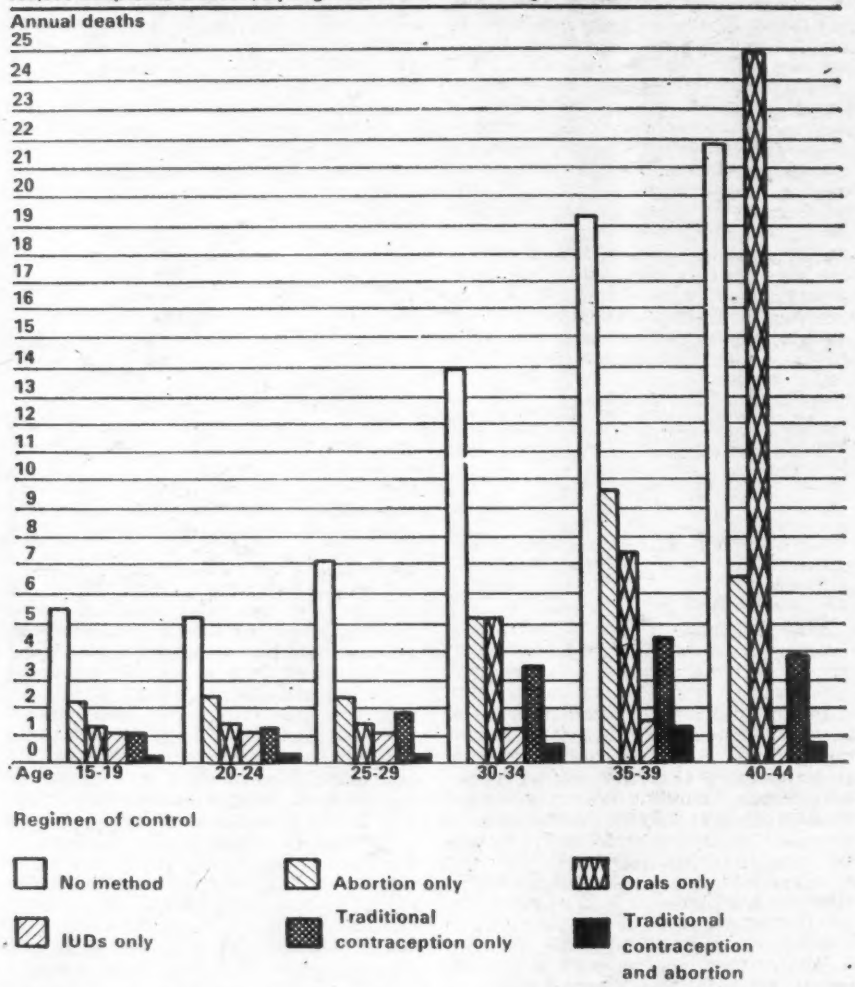
TABLE 4

SUMMARY OF RELATIVE RISK OF THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS IN ORAL CONTRACEPTIVE USERS COMPARED TO NONUSERS

	Relative risk, times greater
Idiopathic thromboembolic disease	4–11
Post surgery thromboembolic complications	4–6
Thrombotic stroke	4–9.5
Hemorrhagic stroke	2
Heart attack (fatal) (age 30–39)	2.8
Heart attack (fatal) (age 40–44)	2.8
Heart attack (nonfatal) (age 30–39)	2.7
Heart attack (nonfatal) (age 40–44)	5.7

The available data from a variety of sources have been analyzed (Ref. 14) to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic diease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below (Ref. 14). The study concluded that the mortality associated with all methods of birth control is low compared to the risk of childbirth, with the exception of oral contraceptives in women over 40, and that the lowest mortality is associated with the condom or diaphragm backed up by early abortion.

Figure 1. Annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women, by regimen of control and age of woman.



The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. The use of oral contraceptives in women in this age group is not recommended.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A four- to six-fold increased risk of post surgery thromboembolic complications has been reported in oral contraceptive users (refs. 15 and 16). If feasible, oral contraceptives should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions.* There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; sudden onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma.* Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestins, none currently marketed, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs.

In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in post menopausal women (Refs. 17, 18, and 19). One publication (Ref. 20) reported on the first 21 cases submitted by physicians to a registry of cases of adenocarminoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occured in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestin-only oral contraceptives.

Several studies (Refs. 8 and 21 through 24) have found no increase in breast cancer in women taking oral contraceptives or estrogens. One study (Ref. 25), however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users or oral contraceptives has been well-documented (Refs. 8, 21, 25, 26, and 27).

In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception.

4. *Hepatic Adenoma.*

Benign hepatic adenomas appear to be associated with the use of oral contraceptives (Refs. 28, 29, and 30). Although benign, and rare, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives, although one study relates risk with duration of use of the contraceptive (Ref. 30). While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Use in Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring.*

The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later

life a form of vaginal or cervical cancer that is ordinarily extremely rare (Refs. 31 and 32). This risk has been estimated as not greater than 4 per 1,000 exposures (Ref. 33). Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix (Refs. 34 through 38). Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb-reduction defects (Refs. 39 through 42). One case control study (Ref. 42) has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births.

In the past, female sex homones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestins are effective for these uses.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contracteptives (Ref. 43). Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period, and further use of oral contractptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks.

It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months.

The administration of progestin-only or progestin-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gall Bladder Disease.*

Studies (Refs. 8 and 23) report a doubling of the risk of surgically confirmed gall bladder disease in users of oral contraceptives or estrogen for 2 or more years.

7. *Carbohydrate and Lipid Metabolic Effects.*

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives (Ref. 44). The clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure.*

An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women, hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives (Ref. 26).

9. *Headache.*

The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

10. *Bleeding Irregularities.*

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Following paragraph to be inserted for progestin-only oral contraceptives:

An alteration in menstrual patterns is likely to occur in women using progestin-only oral contraceptives. The amount and duration of flow, cycle length, breakthrough bleeding, spotting and amenorrhea will probably be quite variable. Bleeding irregularities occur more frequently with the use of progestin-only oral contraceptives than with the combinations and the dropout rate due to such conditions is higher.

Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods.

11. *Ectopic Pregnancy.*

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. However, in oral contraceptive failures, the ratio of ectopic to intrauterine pregnancies is higher than in women who are not receiving oral contraceptives, since the drugs are more effective in preventing intrauterine than ectopic pregnancies. The higher ectopic-intrauterine ratio has been reported with both combination products and progestin-only oral contraceptives.

12. *Breast Feeding.*

Oral contraceptives given in the postpartum period interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs (Ref. 45). The effects, if any, on the breast fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned.

PRECAUTIONS

GENERAL

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than 1 year without another physical examination being performed.

2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size.

3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine if the symptom is drug related.

4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.

7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined.

8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.

10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

d. Decreased pregnanediol excretion.

e. Reduced response to metyrapone test.

INFORMATION FOR THE PATIENT

(See Patient Package Insert below.)

DRUG INTERACTIONS

(Manufacturer to supply information on clinically significant drug-drug interactions.)

CARCINOGENESIS

See Warnings section for information on the carcinogenic potential or oral contraceptives.

PREGNANCY

Pregnancy category X. See Contraindications and Warnings.

NURSING MOTHERS

See Warnings.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see Warnings):

Thrombophlebitis.
Pulmonary embolism.
Coronary thrombosis.
Cerebral thrombosis.
Cerebral hemorrhage.
Hypertension.
Gall bladder disease.
Congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

Mesenteric thrombosis.
Benign hepatomas.
Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related:

Nausea, usually the most common adverse.
Vomiting, reaction, occurring in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occassionally.
Gastrointestinal symptoms (such as abdominal cramps and bloating).
Breakthrough bleeding.
Spotting.
Change in menstrual flow.
Dysmenorrhea.
A memorrhea during and after treatment.
Temporary infertility after discontinuance of treatment.
Edema.
Chloasma or melasma which may persist.
Breast changes: tenderness, enlargement, and secretion.
Change in weight (increase or decrease).
Change in cervical erosion and cervical secretion.
Possible diminution in lactation when given immediately postpartum.
Cholestatic jaundice.
Migraine.
Increase in size of uterine leiomyomata.
Rash (allegric).
Mental depression.
Reduced tolerance to carbohydrates.
Vaginal candidiasis.

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted:

Premenstrual-like syndrome.
Intolerance to contact lenses.
Change in corneal curvature (steepening).
Cataracts.
Changes in libido.
Chorea.
Changes in appetite.
Cystitis-like syndrome.
Headache.
Nervousness.
Dizziness.
Hirsutism.
Loss of scalp hair.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Vaginitis.
Porphyria.
Impaired renal function.

ACUTE OVERDOSE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, (insert name of drug) must be taken exactly as directed and at intervals not exceeding 24 hours.

(Manufacturer to supply information on routine administration and specific instructions on handling problems such as breakthrough bleeding, amenorrhea, etc.)

Use of oral contraceptives in the event of a missed menstrual period:

1. If the patient has not adhered to the prescribed dosage regimen, the possibility of pregnancy should be considered after the first missed period (or after 45 days from the last menstrual period if the progestin-only oral contraceptives are used) and oral contraceptives should be withheld until pregnancy has been ruled out.

2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

HOW SUPPLIED

(Manufacturers to supply information on available dosage forms, potency, color, and packaging.)

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The patient labeling for oral contraceptives drug products is set forth below:

Brief Summary Patient Package Insert

Oral contraceptives taken as directed are about 99% effective in preventing pregnancy. (The mini-pill, however, is somewhat less effective.) Forgetting to take your pills increases the chance of pregnancy.

Women who have or have had clotting disorders, cancer of the breast or sex organs, unexplained vaginal bleeding, a stroke, heart attack, angina pectoris, or who suspect they may be pregnant should not use oral contraceptives. Birth control pills are not recommended for women past the age of 40 because they increase the risk of heart attacks.

Most side effects of the pill are not serious. The most common side effects are nausea, vomiting, bleeding between menstrual periods, weight gain, and breast tenderness. However, proper use of oral contraceptives requires that they be taken under your doctor's continuous supervision, because they can be associated with serious side effects which may be fatal. Fortunately, these occur very infrequently. The serious side effects are:

1. Blood clots in the legs, lungs, brain, heart or other organs.
2. Liver tumors, which may rupture and cause severe bleeding.
3. Birth defects if the pill is taken while you are pregnant.
4. High blood pressure.
5. Gallbladder disease.

Notify your doctor if you notice any unusual physical disturbance while taking the pill.

Although the estrogen in oral contraceptives causes breast cancer and other cancers in certain animals, it is not known whether or not oral contraceptives can cause cancer in humans. At this time there is no definite evidence that they do.

The leaflet given you with your supply of pills discusses in much more detail the benefits and risks of oral contraceptives. It also provides information on other forms of contraception. Read it carefully. If you have any questions, consult your doctor.

Caution. Oral contraceptives are of no value in the prevention or treatment of venereal disease.

Detailed Patient Labeling

What You Should Know About Oral Contraceptives

Oral contraceptives ("the pill") are the most effective way (except for sterilization) to prevent pregnancy. They are also convenient and, for most women, free of serious or unpleasant side effects. Oral contraceptives must always be taken under the continuous supervision of a physician.

It is important that any woman who considers using an oral contraceptive understand the risks involved. Although the oral contraceptives have important advantages over other methods of contraception, they have certain risks that no other method has. Only you can decide whether the advantages are worth these risks. This leaflet will tell you about the most important risks. It will explain how you can help your doctor prescribe the pill as safely as possible by telling him about yourself and being alert for the earliest signs of trouble. And it will tell you how to use the pill properly, so that it will be as effective as possible. There is more detailed information available in the leaflet prepared for doctors. Your pharmacist can show you a copy; you may need your doctor's help in understanding parts of it.

Who Should Not Use Oral Contraceptives

A. If you have any of the following conditions you should not use the pill:

1. Clots in the legs or lungs.
2. Angina pectoris.
3. Known or suspected cancer of the breast or sex organs.

4. Unusual vaginal bleeding that has not yet been diagnosed.

5. Known or suspected pregnancy.

B. If you have had any of the following conditions you should not use the pill:

1. Heart attack or stroke.

2. Clots in the legs or lungs.

C. Although it is your decision, it is recommended that if you are over 40 years old you do not use the pill because of an increased risk of heart attacks from the pill.

DECIDING TO USE ORAL CONTRACEPTIVES

If you do not have any of the conditions listed above and are thinking about using oral contraceptives, to help you decide, you need information about the advantages and risks of oral contraceptives and of other contraceptive methods as well. This leaflet describes the advantages and risks of oral contraceptives. Except for the IUD and abortion, which have their own exclusive risks, the only risks of other methods of contraception are those due to pregnancy should the method fail or not be used conscientiously. Your doctor can answer questions you may have with respect to other methods of contraception. He can also answer any questions you may have after reading this leaflet on oral contraceptives.

1. What Oral Contraceptives Are and How They Work. Oral Contraceptives are of two types. The most common, often simply called "the pill" is a combination of an estrogen and a progestin, the two kinds of female hormones. The amount of estrogen and progestin can vary, but the amount of estrogen is most important because both the effectiveness and some of the dangers of oral contraceptives are related to the amount of estrogen. This kind of oral contraceptive works principally by preventing release of an egg from the ovary. When the amount of estrogen is 50 micrograms or more, and the pill is taken as directed, oral contraceptives are more than 99% effective (i.e., there would be less than one pregnancy if 100 women used the pill for 1 year). Pills that contain 20 to 35 micrograms of estrogen vary slightly in effectiveness, ranging from 98% to more than 99% effective. (Manufacturer may insert pregnancy rate for his product found in clinical trials, if product is a combination).

The second type of oral contraceptive, often called the "mini-pill", contains only a progestin. It works in part by preventing release of an egg from the ovary but also by keeping sperm from reaching the egg and by making the uterus (womb) less receptive to any fertilized egg that reaches it. The mini-pill is less effective than the combination oral contraceptive, about 97% effective. (Manufacturer may insert pregnancy rate for his product found in clinical trials if product is a progestin-only oral contraceptive.) In addition, the progestin-only pill has a tendency to cause irregular bleeding which may be quite inconvenient, or cessation of bleeding entirely. The progestin-only pill is used despite its lower effectiveness in the hope that it will prove not to have some of the serious side effects of the estrogen-containing pill (see below) but it is not yet certain that the mini-pill does in fact have fewer serious side effects. The discussion below, while based mainly on information about the combination pills, should be considered to apply as well to the mini-pill.

2. Other Ways to Prevent Pregnancy. As this leaflet will explain, oral contraceptives have several serious risks. Other methods of contraception have lesser risks or none at all. They are also less effective than oral contraceptives, but, used properly, may be effective enough for many women. The following table gives reported pregnancy rates (the number of women out of 100 who would become pregnant in 1 year) for these methods:

PREGNANCIES PER 100 WOMEN PER YEAR

	Percent effective
Intrauterine device (IUD), 2–3. That is,	97–98
Condom (rubber), 6–13	87–94
Diaphragm with cream or jelly, 2–33	67–98
Coitus interruptus (withdrawal), 6–16	84–94
Rhythm, 6–19	81–94
Foams and jellies alone, 38–42	58–62
No contraception, 60–80.	

The figures (except for the IUD) vary widely because people differ in how well they use each method. Very faithful users of the condom (rubber), coitus interruptus (withdrawal), or rhythm may achieve lower pregnancy rates than those given above, which are the average results for large groups of women. Conscientious use of the diaphragm along with cream or jelly is reported to be 98% effective. Except for the IUD, effective use of these methods requires somewhat more effort than simply taking a single pill every morning, but it is an effort that many couples undertake successfully. Your doctor can tell you a great deal more about these methods of contraception.

3. The Dangers of Oral Contraceptives.

a. *Abnormal blood clotting.* Blood clots (in various blood vessels of the body) are the most common of the serious side effects of oral contraceptives. A clot can result in a stroke (if the clot is in the brain), a heart attack (if the clot is in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impairment of vision in that eye. There is evidence that the risk of clotting increases with higher estrogen doses. It is therefore important to keep the dose of estrogen as low as possible, so long as the oral contraceptive used has an acceptable pregnancy rate and doesn't cause unacceptable changes in the menstrual pattern.

The risk of abnormal clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age, about 1 in 20,000 would be hospitalized each year. For women under 35 who use oral contraceptives the risk of death due to lung clots or stroke is about 1 in 66,000 each year; among nonusers of this age, the risk of death would be 1 in 500,000 each year. For women 35 and over, users would have a 1-in-25,000 risk of death each year, compared with 1-in-200,000 for nonusers.

Even without the pill the risk of having a heart attack increases with age and is also increased by such heart attack risk factors as high blood pressure, high cholesterol, obesity, diabetes, and cigarette smoking. Oral contraceptives further increase the risk of heart attack 3 to 5 times. It is estimated that users of oral contraceptives age 40 to 44 have about a 1-in-1,000 chance each year of having a heart attack, compared with a 1-in-5,000 chance in nonusers. Users age 30 to 39 would have a 1-in-10,000 risk, while nonusers in this age group would have about a 1-in-25,000 risk. These are average figures. If you have none of the heart attack risk factors mentioned above, you will have a smaller risk than is listed. If you have several risk factors, you will have a greater risk than average.

Because of the increased risk of heart attacks, oral contraceptives are not recommended for women over 40. They should never be used at any age by women who have had a stroke, a heart attack, or angina pectoris, or who have had blood clots in the legs or lungs or elsewhere.

b. *Formation of tumors.* When certain animals are given female sex hormones continuously for long periods, cancers may develop in the breast, cervix, vagina, and liver.

No proof exists at present that oral contraceptives cause cancer in humans, but it remains possible they will be discovered in the future to do so. Several studies have found no increase in breast cancer in users, although one study suggested oral contraceptives might cause an increase in breast cancer in women who already have benign breast disease (e.g., cysts).

Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms or who were exposed to the estrogen, stilbestrol, during their mother's pregnancy must be followed very closely by their doctors if they choose to use oral contraceptives instead of another method of contraception. Many studies have shown that women taking oral contraceptives have less risk of getting benign breast disease than those who have not used oral contraceptives. Recently, strong evidence has emerged that estrogens (one component of oral contraceptives), when given for periods of more than one year to women after the menopause, increase the risk of cancer of the uterus (womb). There is also some evidence that a kind of oral contraceptive which is no longer marketed, the se-

quential oral contraceptive, may increase the risk of cancer of the uterus. There remtains no evidence, however, that the oral contraceptives now available increase the risk of this cancer.

Oral contraceptives do cause, very rarely, a benign (non-malignant) tumor of the liver. These tumors do not spread, but they may rupture and cause internal bleeding, which may be fatal. A few cases of cancer of the liver have been reported in women using oral contraceptives, but it is not yet known whether the drug caused them.

c. *Dangers to a developing child if oral contraceptives are used in pregnancy.* Oral contraceptives should not be taken by pregnant women because they may damage the developing child. They cause an increased risk of heart defects and limb defects in the child. In addition, the developing female child whose mother has received DES (diethylstilbestrol), an estrogen, during pregnancy has a risk of getting cancer of the vagina or cervix in her teens or young adulthood. This risk is estimated to be not more than 4 in 1,000. It is possible that other estrogens, such as the estrogens in oral contraceptives, could have the same effect in the female child if the mother takes them during pregnancy.

If you stop taking oral contraceptives to become pregnant, use another method of contraception for up to 3 months. The reason for this is that there is evidence from studies in women who have had "miscarriages" soon after stopping the pill, that the lost fetuses are more likely to be abnormal. Whether there is an overall increase in "miscarriage" in women who become pregnant soon after stopping the pill as compared with women who do not use the pill is not known, but it is possible that there may be.

d. *Gallbladder disease.* Women who have used oral contraceptives for 2 years or longer have twice as great a risk as nonusers of having gallbladder disease requiring surgery.

e. *Other side effects of oral contraceptives.* Some women using oral contraceptives experience unpleasant side effects that are not dangerous and are not likely to damage their health. Some of these may be temporary. Your breasts may feel tender, nausea and vomiting may occur, you may gain or lose weight, and your ankles may swell. A spotty darkening of the skin, particularly of the face, is possible and may persist. You may notice unexpected vaginal bleeding or changes in your menstrual period.

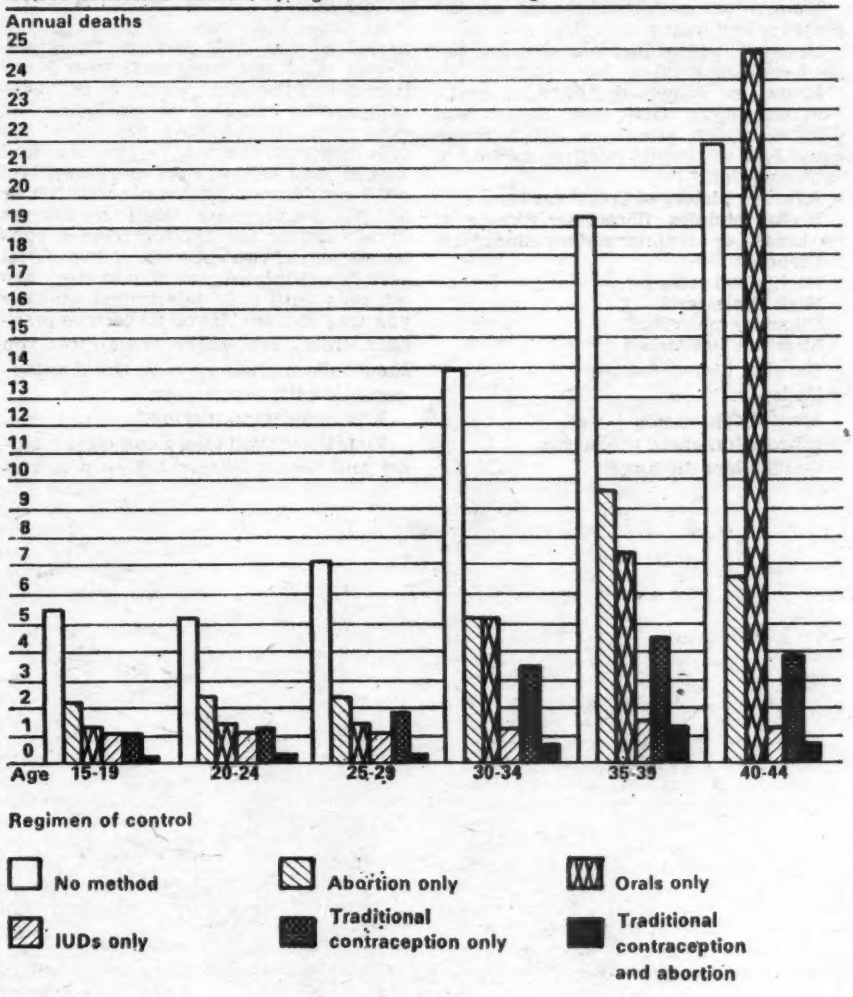
More serious side effects include worsening of migraine, epilepsy, and kidney or heart disease because of a tendency for water to be retained in the body when oral contraceptives are used. Other side effects are growth of preexisting fibroid tumors of the uterus; mental depression; and liver problems with jaundice (yellowing of the skin). Your doctor may find that levels of sugar and fatty substances in your blood are elevated; the long-term effects of these changes are not known. Some women develop high blood pressure while taking oral contraceptives, which ordinarily returns to the original levels when the oral contraceptive is stopped.

Other reactions, although not proved to be caused by oral contraceptives, are occasionally reported. These include more frequent urination and some discomfort when urinating, kidney disease, nervousness, dizziness, some loss of scalp hair, an increase in body hair, an increase or decrease in sex drive, appetite changes, cataracts, and a need for a change in contact lens prescription or inability to use contract lenses.

After you stop using oral contraceptives, there may be a delay before you are able to become pregnant. As discussed previously, you should wait a few months after stopping the pill before you try to become pregnant. During these few months, use another form of contraception. You should consult your physician before resuming use of oral contraceptives after childbirth, especially if you plan to nurse your baby. Drugs in oral contraceptives are known to appear in the milk, and the long-range effect on infants is not known at this time. Furthermore, oral contraceptives may cause a decrease in your milk supply as well as in the quality of the milk.

4. Comparison of the Risks of Oral Contraceptives and Other Contraceptive Methods. The many studies on the risks and effectiveness of oral contraceptives and other methods of contraception have been analyzed to estimate the risk of death associated with various methods of contraception. This risk has two parts: (a) the risk of the method itself (e.g., the risk that oral contraceptives will cause death due to abnormal clotting), and (b) the risk of death due to pregnancy or abortion in the event the method fails. The results of this analysis are shown in the bar graph below. The height of the bars is the number of deaths per 100,000 women each year. There are six sets of bars, each set referring to a specific age group of women. Within each set of bars, there is a single bar for each of six different contraceptive methods. ("Traditional contraception" means diaphragm or condom.)

Figure 1. Annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women, by regimen of control and age of woman.



This analysis is based on present knowledge and new information could, of course, alter it. The analysis shows that the risk of death from all methods of birth control is low compared to the risks of childbirth, *except for oral contraceptives in women over 40*. It shows that the lowest risk of death is associated with the condom or diaphragm (traditional contraception) backed up by early abortion in case of failure of the condom or diaphragm to prevent pregnancy. Also, at any age the risk of death (due to unexpected pregnancy) from use of traditional contraception even without a backup of abortion is generally the same as, or less than, that from use of oral contraceptives.

HOW TO USE ORAL CONTRACEPTIVES AS SAFELY AND EFFECTIVELY AS POSSIBLE, ONCE YOU HAVE DECIDED TO USE THEM

1. What to Tell your Doctor.

You can make use of the pill as safely as possible, by telling your doctor if you have any of the following:

a. Conditions that mean you should not use oral contraceptives:

Clots in the legs or lungs.

Clots in the legs or lungs in the past.

A stroke, heart attack, or angina pectoris.

Known or suspected cancer of the breast or sex organs.

Unusual vaginal bleeding that has not yet been diagnosed.

Known or suspected pregnancy.

b. Conditions that your doctor will want to watch closely or which might cause him to suggest another method of contraception:

A family history of breast cancer.

Breast nodules, fibrocystic disease of the breast, or an abnormal mammogram.

Diabetes.

High blood pressure.

High cholesterol.

Cigarette smoking.

Migraine headaches.

Heart or kidney disease.

Epilepsy.

Mental depression.

Fibroid tumors of the uterus.

Gallbladder disease.

c. Once you are using oral contraceptives, you should be alert for signs of a serious adverse effect and call your doctor if they occur:

Sharp pain in the chest, coughing blood, or sudden shortness of breath (indicating possible clots in the lungs).

Pain in the calf (possible clot in the leg).

Crushing chest pain or heaviness (indicating possible heart attack).

Sudden severe headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg (indicating a possible stroke).

Sudden partial or complete loss of vision (indicating a possible clot in the eye).

Breast lumps (you should ask your doctor to show you how to examine your own breasts).

Severe pain in the abdomen (indicating a possible ruptured tumor of the liver).

Severe depression.

Yellowing of the skin (jaundice).

2. How to Take the Pill So That It Is Most Effective.

(Manufacturer to supply information on dosage and administration and what to do if patient has forgotten to take one or two pills.)

At times there may be no menstrual period after a cycle of pills. Therefore, if you miss one menstrual period but have taken the pills *exactly as you were suppsoed to*, continue as usual into the next cycle. If you have not taken the pills correctly, *you may be pregnant* and should stop taking oral contraceptives until your doctor determines whether or not you are pregnant. Until you can get to your doctor, use another form of contraception. If two consecutive menstrual periods are missed, you should stop taking pills until it is determined whether you are pregnant. If you do become pregnant while using oral contraceptives, you should discuss the risks to the developing child with your doctor.

3. Periodic Examination.

Your doctor will take a complete medical and family history before prescribing oral contraceptives. At that time and about once a year thereafter, he will generally examine your blood pressure, breasts, abdomen, and pelvic organs (including a Papanicolaou smear).

SUMMARY

Oral contraceptives are the most effective method, except sterilization, for preventing pregnancy. Other methods, when used conscientiously, are also very effective and have fewer risks. The serious risks of oral contraceptives are uncommon and the "pill" is a very convenient method of preventing pregnancy.

If you have certain conditions or have had these conditions in the past, you should not use oral contraceptives because the risk is too great. These conditions are listed in the booklet. If you do not have these conditions, and decide to use the "pill," please read the booklet carefully so that you can use the "pill" most safely and effectively.

Oral contraceptives are not recommended for women over 40 years of age.

Interested persons may, on or before February 7, 1977 submit to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, written comments (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding the physician and patient labeling. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

(Secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: December 3, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc.76-36030 Filed 12-3-76;1:01 pm]